Mental Health Series

The Placebo: Promise and Compromise

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INTRODUCTION

The common definition for the word placebo is an 'inert substance.' The Food and Drug Administration (FDA) defines placebo as "an inactive substance that may resemble an active agent but has no medical value." With that definition, it is reasonable to conclude that using and prescribing a placebo would not produce an active reaction, response or effect. Medical research uses placebo-controlled trials in which two groups are administered a treatment: one group receives the active treatment and the other receives an inactive treatment, the placebo.[1,2] Placebo groups ensure validity in trials that result in not finding differences between investigational and standard treatments.[3] Even though the double-blind, randomized, placebo-controlled trial is the accepted standard of medical research, placebo use in trials remains an ethical controversy for many.[2] The inherent issue is the randomized, placebo-controlled trial could compromise sufficient quality of care for some patients today against the promise of improved care for the patient of tomorrow.[4]

PLACEBO AND CLINICAL TRIALS

Robert DeLap, MD, head of one of the FDA's Offices of Drug Evaluation, has clarified the "FDA doesn't require that a drug study include a placebo-control group … only that its design be capable of establishing a drug's safety and effectiveness." However, in FDA literature, the placebo is considered "the fastest and surest way to demonstrate therapeutic effectiveness of new products."[6,7]

The 1938 Federal Food, Drug, and Cosmetic Act authorized the FDA to obtain reports of 'adverse reactions' on drugs marketed to the public to assure the "efficacy and safety" of drugs placed on the market for sale to the public. During the 1940s and 1950s, Harry Gold, a pharmacologist, designed and established a standardized procedure for research trials. Through lectures and publications this standardized procedure, called double-blind, placebo-controlled, became the "gold standard" for clinical trials.[8,9]

As the gold standard for clinical research became widely used, the FDA began requiring at least two placebo-controlled trials with positive results in order to authorize a drug indication, regardless of how many trials fail to demonstrate the drug's superiority to the placebo. The FDA initially recommended that safety and efficacy studies of new drugs use a double-blind design with placebo-controls which subsequently became the guidelines of clinical trials in the 1970s. Eventually, the FDA came to required these procedures, whenever ethical and feasible. The FDA also became aware that future revisions might need to be developed and that guidelines have to continuously be adjusted, addressing the controversy surrounding the practice of using a placebo in clinical research.[10,6,9]

ETHICAL CONTROVERSY

Critics of the placebo-controlled trial say depriving patients of available therapy is unethical.[11] Placebo-controls raise questions concerning the ethical principles of beneficence and human autonomy, even though they are effective in preventing many forms of bias.[12] The American Medical Association (AMA), along with the FDA, supports the use of placebo-controls since they have been proven to be pivotal in establishing the safety and efficacy of new drugs.[11] Other supporters say that active control trials, the primary alternatives, are not easily interpreted because both the active control and the experimental treatment may display signs of the placebo effects, making elimination of the placebo meaningless. When active control studies fail to prove a difference between study groups, multiple conclusions can be reached: both drugs in question are effective; neither is effective; or the criteria for an "effective" drug could not be established. In addition, only placebo-controlled trials can show that a drug's benefits go beyond psychological ones. The placebo-control effectively motivates researchers to avoid any carelessness while obtaining accurate results.[11]

Advocates of placebo-controlled studies and those of active controlled studies do agree that some placebo-controlled studies are unethical, such as when there is effective, life-saving or life-prolonging treatment available and if patients receiving placebo are substantially more likely to suffer serious harm. In addition, advocates of active control must agree that placebo-controls are ethical when minor ailments are the subject of study and when there is minimal risk of harm.[3] However, a fine line exists between what some view as ethical and others view as unethical. Regardless, the use

of placebo-controls allow for increased efficiency, financial feasibility, and an informative nature relative to other methods during trials. In a recent law review, Hoffman proposed the following conditions to ensure patient safety and knowledge during placebo-controlled trials:

(1) each patient is carefully and frequently monitored;

(2) early escape mechanisms exist for patients who suffer adverse consequences related to the lack of active therapy;

(3) the clinical trial duration is as short as possible; and

(4) each participant is clearly informed of and consents to the possibility that he or she will receive placebo rather than standard or experimental treatment.[11]

Other recommendations found in Hoffman's article include limiting the circumstances in which placebo-control is permissible, while minimizing risk to patients, and incorporating these conditions into FDA regulations and guidelines.[11]

CONCLUSION

The "placebo" has been defined as a substance without any value or medical benefit used to compare the value of an active drug, medical device or psychological (as well as neurological) treatment. As a result, placebo-controlled groups are commonly used in clinical trials. Unfortunately, placebo-controls come with many ethical questions; in particular whether the placebo compromises the beneficence and autonomy. However, the advantage of using a placebo in assessing the efficacy of untested medications cannot be ignored. As long as the proper precautions are taken and there are prohibitions in trials that could jeopardize subjects' health or welfare, the placebo will remain an integral part of medical research.[5] ■

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